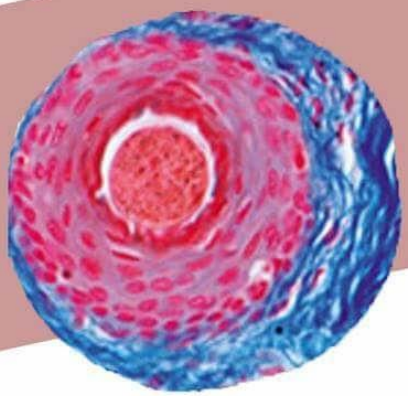
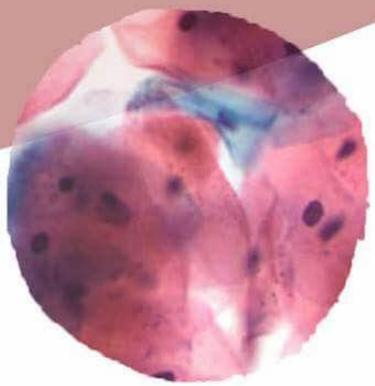
INTRODUCTION TO PATHOLOGY





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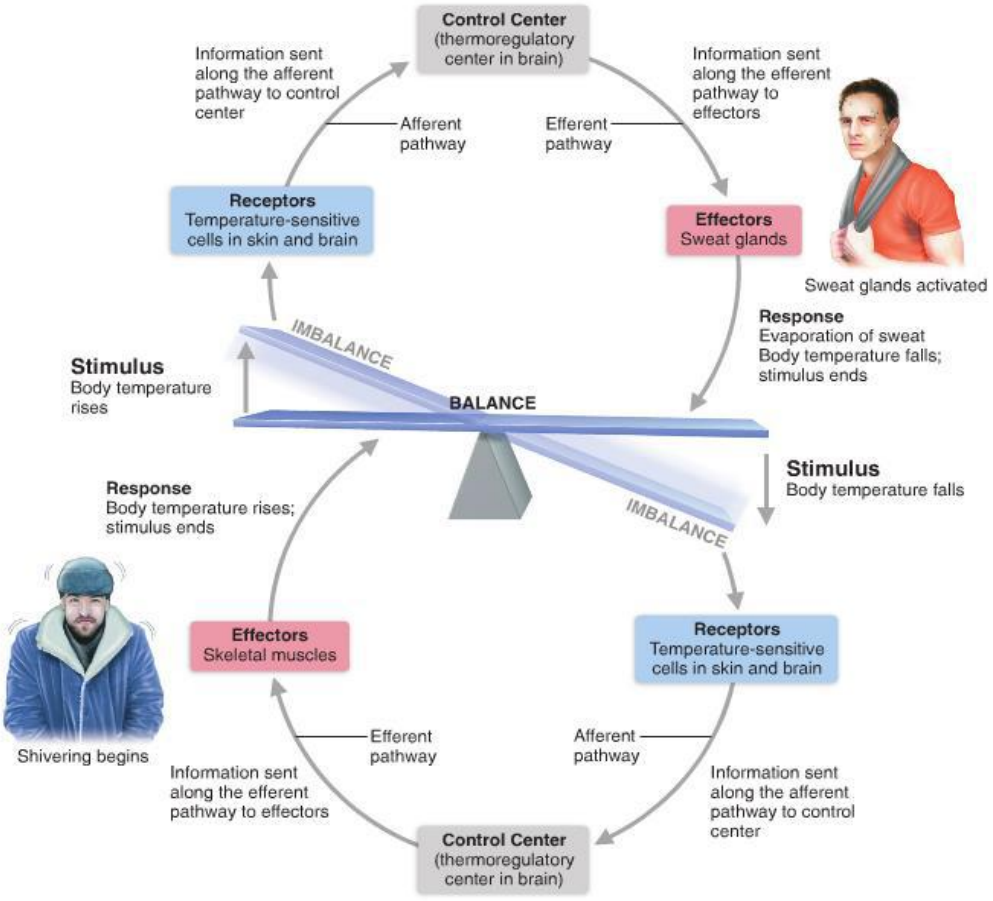
Sheet# 2

What is Homeostasis?

Homeostasis actually indicates balance. It is a range that cells (or the whole body) want to remain in to function normally.

- Is homeostasis considered active or passive? In other words, do cells always want to **react** to the external environment, or could they actively participate in changing their external environment?
  Both, so cells can adapt and also they can change their environment. They can change it because they can produce hormones/growth factors/...and excrete them out (thus affecting something outside). A simple example of your whole body reacting to a stimulus is that if it's hot, you are going to sweat (it is your body's way to cool down/adaptation/passive reaction) to this condition. But also, when it's hot, you'll turn on the fan (active response). Furthermore, if it's cold you'll shiver and wear extra clothes (passive) but also you'll turn on the heating system (active).



** So homeostasis to the cells means that they must be in a narrow physiological range and also affect the external environment to keep themselves in that range. If we're out of this range, the cell would have to adapt.

** If the stimulus-wither physiological or pathological- is mild enough, the cell can adapt, and survive. There are several adaptation mechanisms which include a reversible change in size/number/phenotype/metabolism/function of cells.
** If the stimulus is too strong (severe) or prolonged, the cell could either fail at adaptation or the cell would be **injured** (if stimulus is severe enough).

- One of the adaptation mechanisms is hypertrophy. An example of that: *the heart*. Notice that under normal conditions, your heart cells **cannot** replicate. So in order to adapt to an increased work load, they're going to increase their size (hypertrophy). But how are we going to get an increased work load? (An example of how the heart could get extra stress) ...

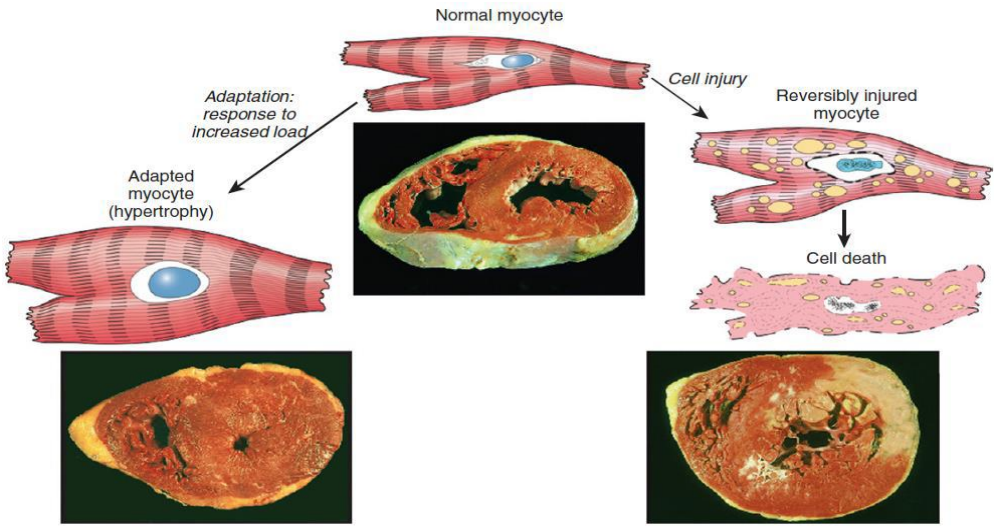
  Note: Generally, if you think of something like running or doing extra work then we'll be more concerned in skeletal muscles rather than the cardiac muscle (because they get a lot more exhausted than the heart) under normal conditions so think *pathologically*…

  →**Blocking of blood vessels,** because your heart is basically a pump; it receives fluid and it sends fluid. So what happens if the output is blocked? If you block the outlet of the heart through aortic valve stenosis –very common in elders-which results in the heart not pumping enough fluid, so it has to work harder to provide the adequate amount of blood to other tissues. The heart will do that by increasing the cell size. However, the problem with increasing the cell size is that the central cavity –inside the heart- is being compromised (due to thicker heart walls the cavity gets smaller). So the harder the heart pumps; the thicker the wall gets; the smaller the cavity gets→which means every time rather than ejecting a 30 mL-for example-,the heart is going to eject half or quarter (smaller ejection fraction). So in addition to your heart now being bigger, having more metabolic requirements, needing more blood, needing more oxygen, it is not able to deliver that oxygen to the body as efficient as it did before. If this goes on for a long time, what's going to happen?

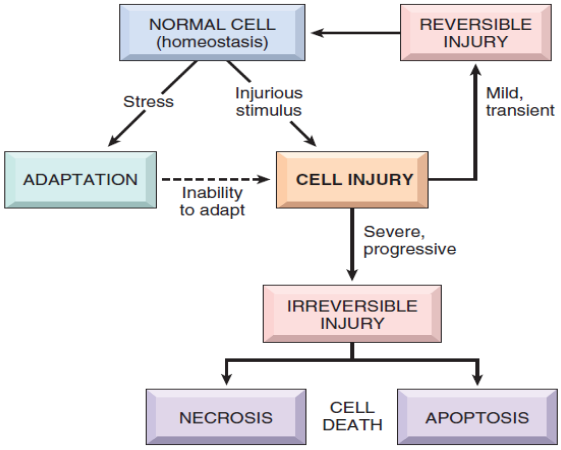
  → Heart failure

  **Note: This all occurs due to occlusion of valves (stenotic valve) of vessels coming out of the heart, not coronary arteries. So when you're talking about outlet obstruction, it's either right ventricle or left ventricle. If left ventricle→ aortic stenosis (common in elders), and if right ventricle, it could lead to pulmonary hypertension(rare), which leads to back pressure and the right ventricle starts having hypertrophy.

- So this is a perfect example of: first, a stress (a pathological one) that caused an organ (heart) to adapt. However, if the stress is long-standing where the organ can no longer keep adapting, it will go into cell injury and failure. In case of the heart, since the cells cannot replicate, the damage is **irreversible**. So the healing will be through fibrosis, and we'll witness myocardial infarctions one after another that will essentially make the heart useless leading to heart failure. (Unless there's a massive coronary occlusion→we'll end up with death).



- So if the stimulus is so severe, you could **immediately** go to cell injury. Cell injury could be reversible or irreversible. (cell injury can also happen if the stimulus is too fast for the cell to adapt)
- Reversible early on cell injury→ some swelling of the cell because the ion pumps have stopped working plus some vacuoles in cytoplasm (fatty change).
- Now what's worse for the heart, even though the injury is reversible, and under the microscope you may or may not see some swelling, is that the **fibers themselves have stopped contracting (**it has lost **function** before it lost viability). In other organs, it's not a big deal, but the heart losing part of its function means it's going to eject less blood, which means the already compromised tissue is going to be further compromised.
- So not only we're thinking about the environment affects the cell, we need to think about the basal state of the cell. For example, if you are a marathon runner, at the beginning of the marathon and you undergo hypoxia (lack of oxygen), you're still fairly early on, you're not exhausted and you don't have a lot of lactic acid accumulation →you can take it. But if you've already run 20 miles and you're going to climb Everest, now you're starting to climb and the oxygen is getting lower and lower, you're going to be affected a lot faster than when you were at the beginning of the marathon.
- It's the same thing for your cells. A cell that has just expended its very last ATP, finished its Glycogen stores, and then you come and add a stressful stimulus to it, it may actually push it directly to cell injury. Whereas another cell perfectly at rest, still got its ATP and still got plenty of energy stores and oxygen stores, when applying the same stress it may just cause it to adapt.

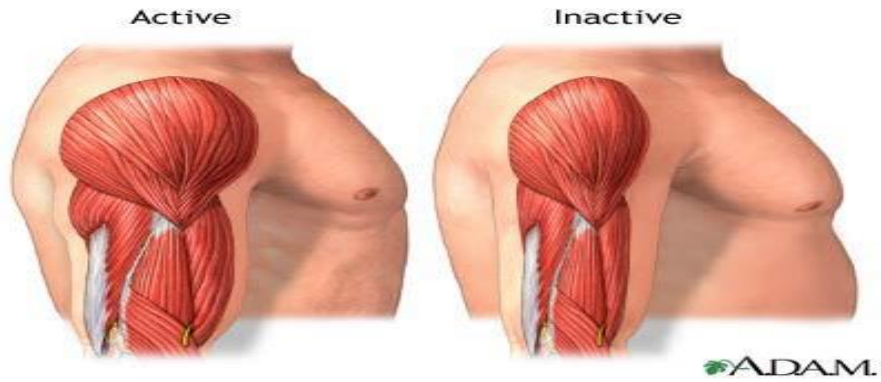


- Let us first look at **adaptation,** which is essentially cells trying to preserve their homeostasis. It's **always reversible,** and it has 4 types:
  1- Hypertrophy: increase in cell size.
  2- Hyperplasia: increase in cell number.
  3- Atrophy: decrease in cell size.
  4- Metaplasia: change in cell type.

- ***Hypertrophy:*** increase in cell size
  Note: Do not get confused when the book mentions pure vs. mixed hypertrophy. When we talk about adaptation as a **cellular process, hypertrophy is **only** increase in cell size. If we take it up to the organ level (if we're talking about organ hypertrophy), it can result from either cellular hypertrophy or hyperplasia so this is mixed organ hypertrophy.

- The reason of cells increasing their size rather than increasing their number is that the cells cannot replicate.
  cardiac muscle cells→cannot replicate
  skeletal muscle cells→cannot replicate
  liver hepatocytes →can replicate
  uterus cells →can replicate
  skin cells →can replicate
  So it depends wither the tissue is a stable tissue or a labile (regenerative) tissue.

- Examples of pure hypertrophy (physiological example): ***Body Building*** and a pathological example is myocardial hypertrophy due to blocked output. A physiological example of mixed hypertrophy is the uterus of a pregnant woman so during pregnancy the uterus (as it can replicate) not only increases cell size but also cell number.



- Bigger cells produce more structural proteins (that's how they get bigger). In case of muscle fibers they produce more actin and myosin, which require more energy, which means they're going to produce more organelles like mitochondria.
- ***Hyperplasia:*** increase in cell number. So we're talking about organs that can proliferate.
- Examples of physiological hyperplasia include the growing process (going through a growth spurt) and also, a female going through puberty experiences hyperplasia in her breast. Furthermore, the uterus and breast of pregnant women also undergo hyperplasia.
- Cancer differs from pathologic hyperplasia. For hyperplasia to occur, growth factors, hormones, etc… must be produced to induce hyperplasia. An example (physiological) is pregnant women; hyperplasia is induced via pregnancy hormones which affect the breast glands and the uterus. But at the end of pregnancy, when the production of pregnancy hormones stops, hyperplasia also stops, and the breast and uterus gradually return to normal. An example of pathologic hyperplasia is that if you have an imbalance between estrogen and progesterone which is (the balance) important for the menstrual cycle, and if you have too much stimulus for the endometrial lining to undergo hyperplasia (gets too thick), there's going to be shedding between the cycles (abnormal menstrual bleeding). If you withdraw this imbalance (give the patient hormones or OCPs-oral contraceptive pills-) you're essentially returning the hormones back into balance→ the hyperplasia stops and the bleeding stops. However, if that was cancer, **even if you take away the stimulus of hyperplasia (growth factors and hormones) the cancer will continue to grow**. **Cancer becomes independent on the growth factors that caused the hyperplasia in the first place.** With that in mind, pathologic hyperplasia is a fertile ground for cancer (it can turn from pathologic hyperplasia to cancer).

  ***QUESTION:* why is there a probability that hyperplasia turns to cancer?
  Answer: Because cancer can result from genetic errors (mutations) in the genetic code. Hyperplasia includes cells proliferating, so there's a need to replicate the DNA for every division, which increases the possibility of getting replication errors. It's

true we have repairing enzymes but they are not 100% accurate, so higher probability of genetic errors→higher probability of cancer.

- There is physiological hyperplasia which is either hormonal (discussed before) or compensatory hyperplasia. One example of that is hepatectomy, so you can donate more than half of your liver and the rest of the liver will detect the reduction in size and function and will start to undergo hyperplasia plus hypertrophy to fill in the gap of the donated liver.
- ***Atrophy:*** a retreat of the cell to a point where it becomes viable again. So it hasn't died; it's still alive and still functioning but retreated to a smaller size with less metabolic demands, less oxygen demand, less (diminished) function (but NOT dead). And this means if you take away the stress, the cell will get back to normal; because by definition atrophy is a reversible process because it is an adaptation (reversible cellular process).
- How can a cell get smaller? Essentially it's getting rid of its own protein. So it's the mark opposite of hypertrophy. Now, it's going to use the protein in the organelles that it has for energy or as building blocks for more essential proteins. So non-essential functions are the first to go, and then the essential functions will keep retreating down to a point at which the cell will fail to adapt and die if the stress that induced atrophy is still there.
- Causes of atrophy:

  1- Disuse atrophy (e.g. arm muscles not being used-after a car accident-for a long time→muscle cells shrink and the organ as a whole shrinks).

  2- Loss of innervations (if a group of muscle cells use innervations→no contraction (essentially like disuse) and you can't use these muscle fibers).

  3- Loss of blood supply (less or no nutrients/less oxygen), which means that cells that are metabolically active are the first to be affected by this, and they're undergoing atrophy trying to preserve their viability. But if it goes on for too long, they die.

  4- Reduction of nutrition. (Because no blood supply is not the only way of reduction of nutrition to tissues; you could be not properly eating, or going through diets where you don't eat essential elements).

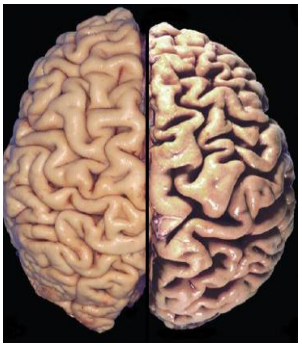
  5- Loss of hormone (A physiological example is menopause. Female sexual organs undergo atrophy, but this doesn't mean that they are not functional-because if we give the proper hormones to an old lady/tried in vitro fertilization she can get pregnant- so the organ is still there and it can work again if we give right hormones).

  6- Aging (the older you get, the weaker your muscles get, the more hunched you get. Also you will start losing your brain cells-brain undergoes atrophy-).
- Mechanism of atrophy: cells start reducing protein synthesis, minimizing it to a point where only viability-essential proteins are made. Now, proteins have a life cycle, so they get normally degraded after a while and the cell will lose proteins, but cells that are desperate will actually activate and degrade its own proteins. This degradation is done by what is called *ubiquitin-proteasome pathway*.

**Ubiquitin is actually a very small protein the cell produces. Enzymes attach this protein onto other proteins, this can affect and change the location of a protein, or change the function of a protein, but more importantly for Ubiquitin-proteasome pathway, it signals for the cell that this protein is no longer required, break it down to its amino acids and use it for something more useful. That's why the proteasome (protein complex) comes in and chops up the labelled protein. Now it's easier to break it to its amino acids.

** Also, cells undergo **Autophagy (self-eating)** on its own organelles. The cell creates a double membrane around an organelle or an area of the cell that it's required for degradation. This autophagosome is going to fuse with a lysosome that contains hydrolytic enzymes which break the organelle to its basic building blocks. So what are we getting? We're getting amino acids –from organelle protein- and also lipids. These amino acids and lipids can be used for energy or for maintenance of cell membrane or other things that are more important than that particular organelle.

- Note that <u>some</u> organs like the brain; if they go too far into atrophy it's very hard to pull them back. So for the brain, it's too hard to repair itself to normal again if it's deeply shrunk.

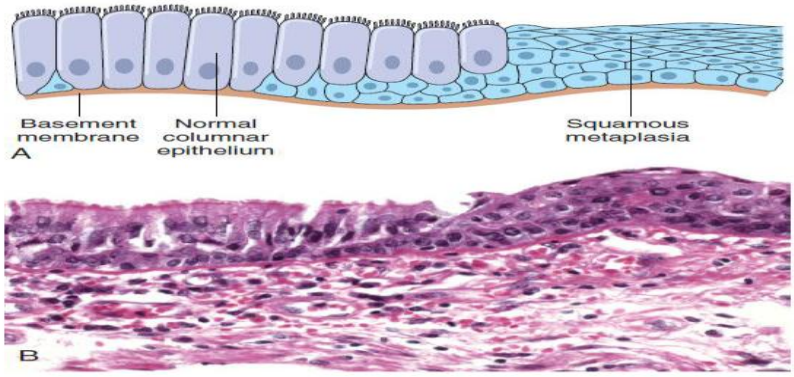


- ***<u>Metaplasia:</u>*** change from one cell type to another cell type that's not supposed to be there. But the other cell/tissue type (the new) will look like a perfectly normal tissue if it was somewhere else in the body (the new tissue exists in the body but elsewhere).

  **So if we take a tissue sample from the esophagus, we'd expect to see non-keratinized stratified squamous epithelium. And if we were to take a sample and it looked like intestinal epithelium (columnar), so unless we're told that this was taken from the esophagus, we're going to assume that this is taken from the intestine. This is Metaplasia.

  On the other hand, dysplasia (discussed later) is a change in cell type into an abnormal shape. **This tissue does not exist anywhere in the body in normal conditions. Whereas in Metaplasia, it's a normal tissue but in the wrong place.

- An example of Metaplasia is the tissue change in the trachea and the entire bronchus due to **smoking**. So when you smoke, you irritate your airways, thus changing from pseudostratified columnar epithelium (ciliated + goblet cells) to stratified squamous epithelium, which are better adapted to smoking. But it's actually a double-edged sword→the price that you're paying is the loss of cilia, which means you can no longer expel anything that is stuck in your bronchus, and no mucus→ so you can't trap toxins and carcinogens early on, and they'll go all the way down into the lungs. An important note is that this way, your lungs suffer from a prolonged exposure to toxins, **WHICH ULTIMATELY MEANS**, that Metaplasia-like hyperplasia- is also a fertile ground for **cancer**.



- Now, Metaplasia could be epithelial (mentioned earlier) or mesechymal.
- **<u>DON'T FORGET:</u>** Metaplasia is a reversible process, because by definition, adaptation is a reversible process.
- The other thing about Metaplasia is that it's not a change in cell type of the mature cells. **The stem cells (cells which produce mature cells) are re-programmed to produce a different type of cells.**

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- Adaptation fails if: so severe/ so prolonged/ so fast stress/ the cell's basal state is already pushed to a limit where it can't continue/ the cell is highly metabolically active and you take something very important for it and it depends on it. Here we move to **cell injury**.
- What do you think would be more severely affected with hypoxia? A neuron or a fat cell?

  ** A neuron, because it's very active, uses a lot of ATP and requires a lot of oxygen. Whereas fat cells are generally dormant-there is some exchange of lipids- but they can withstand hypoxia a lot better than neurons do.
- So think about that when you think about what's the first thing to be saved in a patient who is having a cardiac arrest for example. →***Vital Organs*** (cannot withstand hypoxia and require oxygen the most). E.g. the brain, lungs (you should check if they're functioning well in order to make sure that there's enough oxygen to get to the rest of the vital organs). We'll be worried about the kidneys, because if they're gone off for too long, they might shut down. On the other hand, the liver has got a lot of capacity so we're not so worried about the liver early on. But (brain/any other

neuro-like tissue like retina)→all of these are the first to go. Thus I'm not so worried about tissues like muscles-muscles can withstand a lot of hypoxia and a lot of lactic acid- but I am worried about vital organs like the kidney.

** Am I worried about the cornea?

Answer: cornea (the transparent layer forming the front of the eye) is actually a living tissue but actually DOESN'T have a blood supply. It actually gets its oxygen by diffusion from the atmosphere because there's only a thin film of fluid on the cornea. That is why we're not so worried about it.

*Note: Due to cornea taking its oxygen from the atmosphere, it can actually be transplanted from a dead body to someone alive even if the body is dead a while ago. This is good and effective because cornea doesn't have a blood supply so it won't be rejected and it can live for a long time.

- If we do look at an injury, we're looking for (reversible or irreversible injury), (necrosis or apoptosis). Now reversible injury→not much to be seen under the microscope, mostly some cells swelling and some blebs. Some small, clear lipid vacuoles within the cytoplasm may be revealed. This pattern of nonlethal injury is called **hydropic change** or **vacuolar degeneration**. Irreversible injury once happened, the cells can die in of two ways; either through apoptosis or necrosis. Necrosis is always pathological, whereas Apoptosis can be physiological.

  ** When do we want cells to die off? (When is it physiological?)

  Answer: There are a lot of cases/examples. White blood cells (WBCs) during an infection, they would sometimes sacrifice themselves through apoptosis in order to kill bacteria. More importantly, when you have an infection, WBCs increase in number, and later after the infection is gone, where are these WBCs going to go? They're going to undergo apoptosis to come back to the normal level of WBCs. Another example is during embryogenesis, when creating a blood vessel or any other organ that has a cavity like the esophagus or the stomach or the intestine, what is created first? How are tubes made embryologically? By folding, but what we get is actually a cord-with no cavity-so cells in the middle die off by apoptosis to create a tube.

  ** More about WBCs: How do you think your WBCs recognise bacteria and viruses that are foreign? By specific receptors and production of antibodies, etc...but there are millions of types of bacteria, foreign antigens, allergens, viruses and fungi…so do we have a list in our DNA? No, we don't have enough genes to cover all of them, so we do it through random recombination of genes and we randomly create these antibodies, cell receptors,etc…so it's a random process, which means some of them may not be reactive, while some of them will be reactive and will find that bacteria and get rid of it. Some of them unfortunately will react against your own proteins. So some of the immune cells producing these antibodies like B and T cells must die, so our body induces their death through apoptosis. If these cells don't die→ **Auto-immune diseases.**

Note that when **RBCs die, it's not apoptosis because apoptosis needs an intact nucleus to begin with, but RBCs don't have any nuclei.

- The morphology of necrosis is considerably different than apoptosis. In necrosis, you have a disruption of the cell membrane, cellular contents will leak out, and the mitochondria will look very abnormal. On the other hand, apoptosis→ no membrane leakage, the cell actually divides itself up to little vesicles, and only attracts phagocytes and tells them to come and clear this mess up to make sure that inflammation does not occur. So your WBCs have never seen the inside of your other cells, so any protein or enzyme leak from one cell to the outside will look foreign to these WBCs. That is why necrosis induces inflammation whereas apoptosis (no leakage) will not.
- ***Morphology of cell death :***
- →→If you have a type of cell death that is caused by ischemia, and it produces a wedge shaped area following the blood supply, the tissue architecture is perfectly conserved, but the cell is dying
  First, Since it's cell death, is it apoptosis or necrosis?
  Answer: It is necrosis, the cells have died off and leukocytes' lysosomes and phagocytosis are required for clearance, and cells died due **to loss of blood supply.**
  Second, What type of necrosis is it?
  Answer: **Coagulative Necrosis**.
  Note: This type of necrosis occurs in all solid organs **except** the brain.

- →→The type of necrosis that occurs in the brain, or occurs when there is an infection with a certain bacteria or fungi, and there is liquid involved.
  → Liquefactive Necrosis.
  Note: The reason for why Liquefactive necrosis occurs in the CNS infarcts is not fully understood. All other solid tissues undergo Coagulative necrosis when subjected to ischemia, but the brain liquefies!! Now, for bacterial or fungal infections it is fully understood; WBCs come to the infection site and start phagocytosis, but if there were a lot of bacteria, WBCs start to burst themselves in order to kill them all, so the inflammatory reaction, edema, WBCs and the killed bacteria/fungi make up **pus**.
- →→**Gangrene necrosis**: This is not really a distinct type of cell death, but it's mainly a clinical term. An example is that when you go out and it's snowing, and you are not properly clothed (no gloves/ not proper shoes), and you stay out for too long, you will lose feeling in your extremities (frostbite) and you come back and wonder; why is one of my toes black? It's because the cold has caused a constriction in blood vessels in your extremities, and this loss of blood supply may be long enough and severe enough to push your extremities cells' into necrosis. **So it's a type of Coagulative necrosis, but clinically the term is gangrene (this is a dry gangrene).**
  ** If there is a superimposed infection (bacterial infection for example) to necrotic

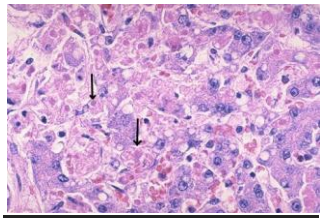
cells (cells died by necrosis), and you start having liquefaction, you'll have a mix between Coagulative and Liquefactive necrosis, which is called a **wet gangrene.** It frequently occurs with patients who have diabetes (diabetic foot /diabetic leg).

- →→**Caseous Necrosis**: (caseous means cheese in Spanish) This type of necrosis is a cheese-like that occurs when there is a granulomatous inflammation. It occurs frequently in tuberculosis.
- →→**Fat Necrosis**: it has two types; **enzymatic fat necrosis**, which occurs when there is the abdominal emergency of acute pancreatitis. Exocrine pancreas produces digestive enzymes, so if the exocrine pancreas undergoes necrosis, these enzymes will be released into the extracellular fluid. They are going to spill out of cells into the peritoneum. The lipases will start breaking down the fat in fat cells in the peritoneum releasing fatty acids out, which in turn react with the extracellular calcium (Ca^{+2}) in a process called **saponification**. If you open the patient up, you'll see white, friable deposits/bits, and you'll know that the pancreas has undergone some necrosis.

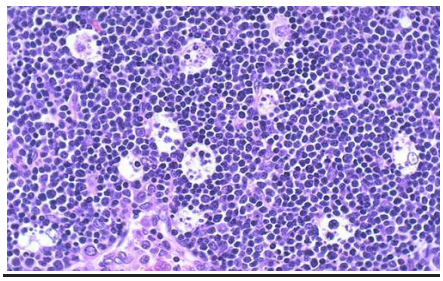
  ** It may already be too late for the patient, that is why acute pancreatitis is an abdominal emergency.

  -The other type of fat necrosis (not in the book) is **traumatic fat necrosis**, which is due to a hit (trauma) to fat cells. Some of them die and release the lipids inside. The area that you really want to be careful about (especially females) is the breasts, because you have bones behind them, and if something hits you there, it will cause some damage. The problem is when cells die they attract calcium, and this is called **dystrophic calcification**. If a patient comes in for a mammogram, one of the signs of breast cancer is micro-calcifications in the breast. If the history is not well-taken (if the patient is not asked wither she ever took a hit on her breast), the patient will be worried about breast cancer (false call).
- →→**Fibrinoid Necrosis:** it's only visible under the light microscope, and it's a result of accumulation of antigens, antibodies and fibrin in a disease called **polyarteritis nodosa**.

- →→**Apoptosis:** This type of cell death does not induce inflammation.



The picture above is pathologic apoptosis (viral hepatitis).



The picture above is apoptosis in the thymus. When the thymus is used for development of T-cells and some of these cells may be self-reacting (they react to your own tissues), we induce them to apoptosis so we don't get auto-immune diseases.

THE END